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Design and Development of Mucoadhesive Film Forming Spray of Lidocaine for Effective Pain Management in Treatment of Periodontal Diseases.

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ABSTRACT – The study was aimed to formulate mucoadhesive film forming spray-containing lidocaine, a local anaesthetic agent which could be easily sprayed into the dental cavity and capable of delivering therapeutic concentration of drug for prolonged period. In the present investigation mucoadhesive film forming spray containing lidocaine was prepared. The prepared formulations were evaluated for various properties such as stickiness, film formation, drying time, spray pattern test, spray angle, in vitro release. The drying time were found to be in the range of (62 – 148 sec). The in-vitro release studies showed different release rate of the formulation. The short term stability studies were conducted and there were no significant changes observed. Hence, site-specific mucoadhesive film forming lidocaine spray is a potential tool for effective pain management in treatment of periodontal diseases.

Keywords – Mucoadhesive film forming spray, Periodontitis, Lidocaine, Eudragit E100, HPMC E15

I. INTRODUCTION –

The word periodontal means "around the tooth". Periodontal diseases are mainly the result of infections and inflammation of the gums, bone that surround, and support the teeth. It is the leading cause of tooth loss and one of the two most serious dangers to oral health. There are about 800 types of bacteria in the mouth cavity, and it has thought that a complex interaction of bacterial infection and human response, influenced by behavioural factors like smoking, can lead to periodontal disease. There are many types of periodontal diseases e.g. Periodontitis, gingivitis, aggressive periodontitis, chronic periodontitis.[1][2][3]

The North American Nursing Diagnosis Association define pain as a condition, through which a person feels and records extreme discomfort or irritating sensation; pain can be reported either by verbal contact or through the descriptors. Pain whether acute or chronic is a phenomenal clinical challenge that has been largely unmet, e.g., pains associated with post dental surgery, tooth pain, and mouth ulcer, etc. The two major classes of analgesics, i.e., NSAIDs and opioids are well known to exert significant adverse effects. [4]

Local anaesthetics present additional advantages over the conventional analgesics. They primarily work by numbing the affected area without causing dizziness as seen with opioids. It bypasses the adverse effects caused by the oral analgesics, provides an instant relief from the pain as well as increases the patient compliance. Nowadays, lidocaine in the form of a various formulation is used for the management of various kinds of pains, such as, post-operative pain, neuropathic pain and dental pain, etc.[5]

The objective of present research project was to explore the application of lidocaine for effective pain management therapy in the treatment of periodontal diseases by designing it's longer activity topical drug delivery system as the presently available marketed pain relief oral spray/gel formulations used for the treatment of periodontal diseases do not provide effective and longer duration pain relief because they get washed away from the site of application soon after their administration. Therefore, it was thought worthwhile in the present studies to develop an oral mucoadhesive film forming spray formulation of lidocaine, which would have longer retention time at site of application and thereby manifest a longer duration of action.[6]

In this present study Eudragit E100 is used as film forming polymer in the formulation and HPMC E15 (hydroxy propyl methyl cellulose E15) was used as mucoadhesive polymer in the formulation. Ethanol and water used as a solvent.[7] [8] [9]

The developed formulation was compared with marketed formulation of lidocaine spray (Xylocaine™).

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II. MATERIAL AND METHODS –

Material - A gift sample of lidocaine was obtained from M/S Zydus Cadila, Ahmedabad, India. Eudragit E100 was obtained from Evonik industries, Germany and HPMC E15 was obtained from Loba chem. pvt. Ltd. All other chemicals used were of analytical grade.

Method - Ethanol was taken in a beaker and accurately weighed eudragit E100 was added into it. Subsequently, stirring was done using magnetic stirrer. After complete dissolution of eudragit E100, lidocaine was added into it with continuous stirring. Accurately weighed HPMC E15 was taken into a separate beaker and dissolved properly by adding purified water. Further, the prepared solution of HPMC E15 was added into the solution of eudragit E100 containing lidocaine and stirred for 30 min on magnetic stirrer. After that the prepared solution was stored in a bottle**.**

Table 1. Formulation of mucoadhesive film forming spray

Components	F1	F2	F3
Lidocaine (%)	1	1	1
Eudragit E100 (%)	2	2	3
HPMC E15 (%)	2	3	3
Ethanol : water	8:2	8:2	8:2

Evaluation parameters of mucoadhesive film forming spray –

Evaluation parameters such as stickiness, film formation, drying time, spray pattern test, in vitro release of prepared mucoadhesive film forming spray were determined.[10]

Stickiness - The stickiness of the film formed was determined by pressing cotton wool on the dry film with low pressure. Depending on the quantity of cotton fibres retained by the film the stickiness was rated high if there was dense accumulation of fibres on the film, medium in presence of thin fibre layer and low if there was an occasional or no adherence of fibres.

Table 2. Stickiness of different formulations

S. No.	Formulation	Observation
1.	F1	Non sticky
2.	F2	sticky
3.	F3	Sticky

Drying time - For the evaluation of drying time, the formulation was applied to the glass sides, After a fixed time period another glass slide was placed on the film without pressure. If no liquid was visible on the glass slide after removal, the film was considered dry. If remains of liquid were visible on the glass slide the experiment was repeated with an increase in drying time. A good film forming spray should have minimum drying time.

Table 3. Drying time of different formulation

S. No.	Formulation	Observation
1.	F1	62 sec
2.	F2	115 sec
3.	F3	148 sec

Spray angle - Spray angle was measured to check the distribution of the formulation onto the application site. The experiment was carried out by colouring the formulation with 1% methyl orange. The white paper was place horizontally at a distance of 15 cm from the nozzle. The radius of the circle formed was recorded and spray angle was calculated,

$$\text{Spray angle}(\emptyset) = \tan^{-1}(h/r)$$

Where h= distance of nozzle from the paper (15 cm)

r = average radius of the circle

Spray pattern test - Spray pattern testing was done to analyse the degree of evenness with which the formulation applied to the surface. Formulation

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was coloured with 1% methyl orange for easy visualization of droplets. The prepared formulation was sprayed onto a white paper at a distance of 2.5-3 cm. A uniform dispersion of droplets on the white paper was considered satisfactory.
As per the different evaluation results were discussed in the study, batch F1 was selected as final batch and their in vitro release was compared with marketed product Xylocaine™.

In-vitro release study –

Studies of in-vitro permeation were performed using dialysis membrane (HiMedia 70) using Franz diffusion cell in phosphate buffer (pH 6.8) at 37 ± 0.5˚C. It consisted of a donor compartment and a receptor compartment. The receptor solution was then agitated by a small magnetic bead at a constant rate of 100-200 rpm. The dialysis membrane was mounted between the donor compartment and the receptor compartment. One puff was sprayed on the dialysis membrane and wait for drying the film. The diffusion cell's receptor compartment was filled with phosphate buffer (pH 6.8). The entire assembly was placed on the magnetic stirrer. A temperature of 37 ± 0.5˚C was maintained. The diffusion fluid was withdrawn at the different time intervals and analysed for drug amount by Shimadzu 1700 double beam UV-visible spectrophotometer at 263 nm.

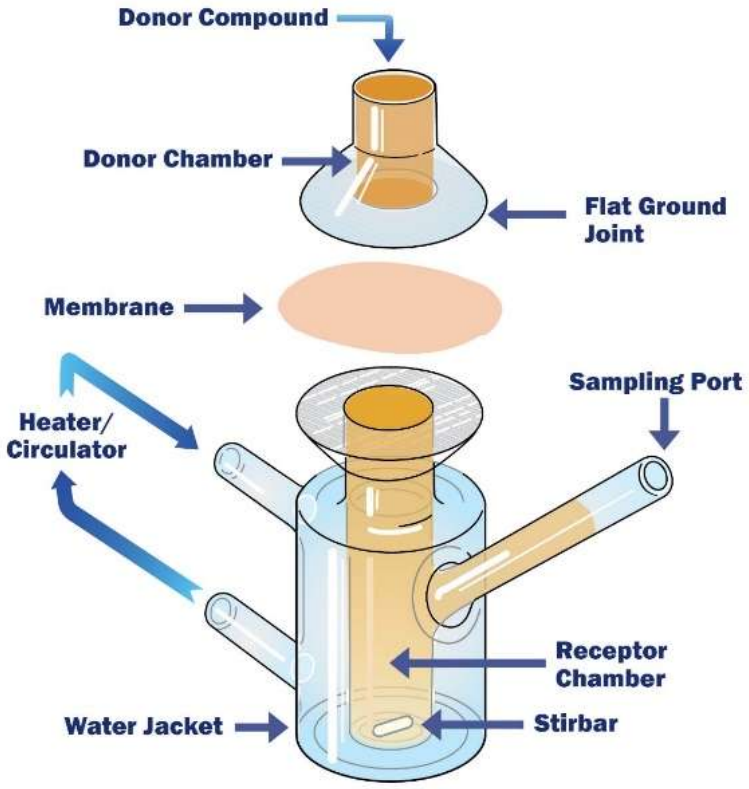

Fig. 1 – Franz diffusion cell

Table 5 . In vitro drug release of marketed spray formulation of lidocaine (Xylocaine™ – Zydus Cadila)

S. No.	Time (Minutes)	Cumulative drug release
1.	0	0
2.	5	9.92
3.	10	13.05
4.	15	15.99
5.	30	17.10
6.	60	18.86
7.	120	20.48
8.	180	21.85

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9.	240	21.91

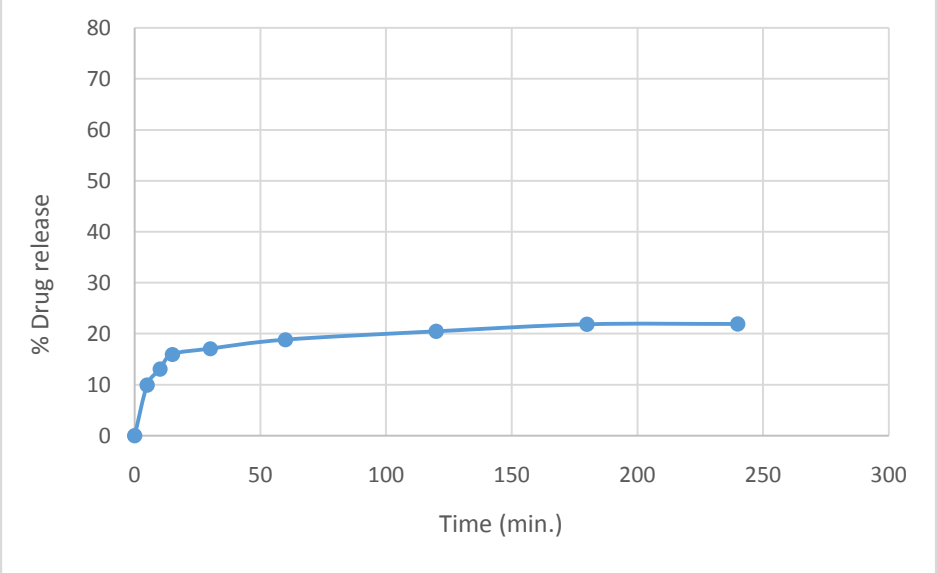

Fig. 2 In vitro drug release of lidocaine from marketed formulation (Xylocaine™ – Zydus Cadila)

S. No.	Time (Minutes)	Cumulative drug release
1.	0	0
2.	5	11.99
3.	10	24.91
4.	15	35.89
5.	30	44.13
6.	60	55.22
7.	120	62.12
8.	180	67.53
9.	240	72.22

Table 6. In vitro drug release of lidocaine from developed mucoadhesive film forming spray formulation (F1)

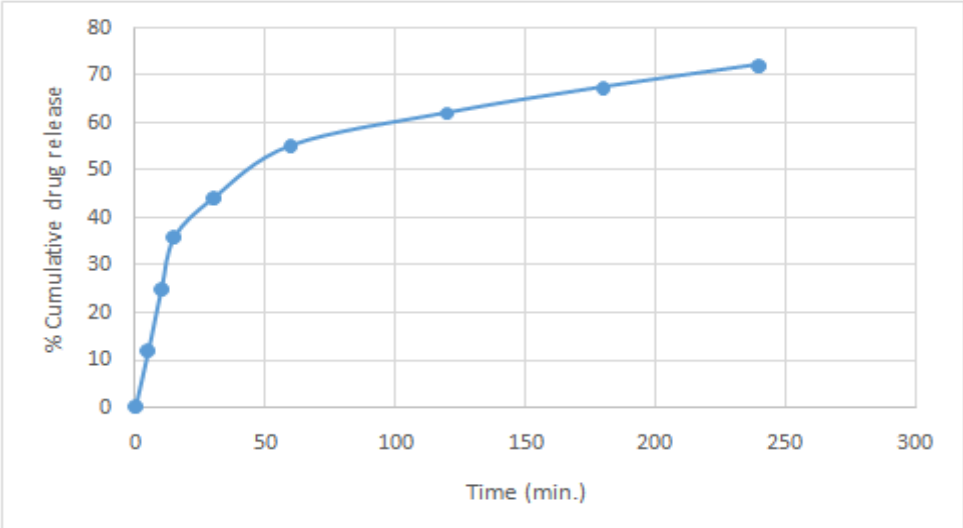

Fig. 3 In vitro drug release from developed mucoadhesive film forming spray formulation

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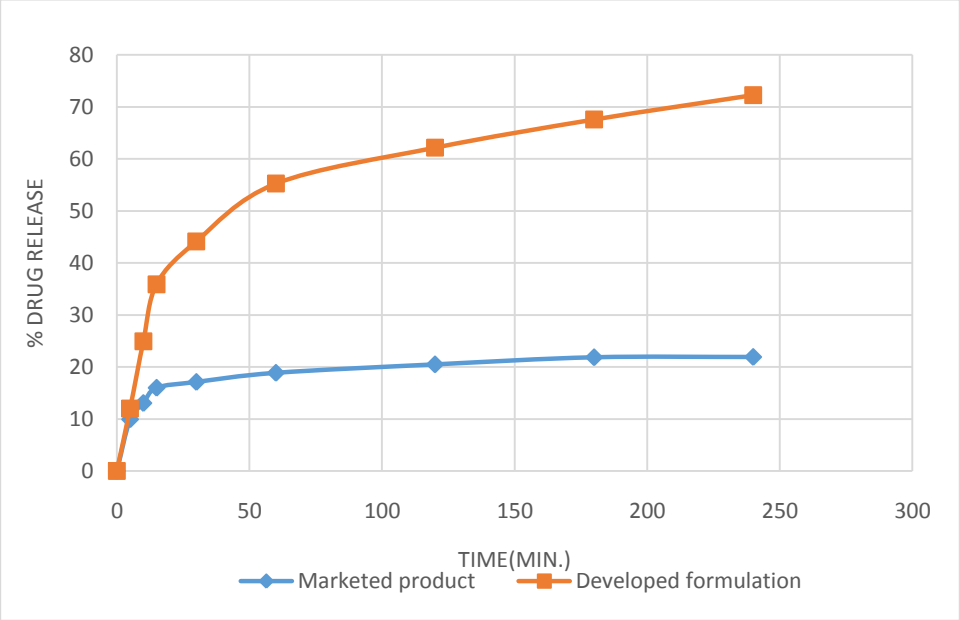

Fig. 4 Comparative in vitro drug release of developed mucoadhesive film forming spray formulation and marketed spray formulation (Xylocaine™ – Zydus Cadila)

III. RESULTS –

The result of present study indicated that HPMC E15 and Eudragit E100 could be subsiquently used as a mucoadhesive and film forming polymer for mucoadhesive film forming spray containing lidocaine. Mucoadhesive film forming spray formulation containing lidocaine had been prepared with satisfactory physiochemical characterizations. On the basis of data obtained from in-vitro drug release studies, F1 is promising formulation suitable for prolong release of lidocaine for the oral cavity use since they exhibited maximum drug permeation.

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